Risk assessment workshop features cutting-edge toxicogenomic research

By Sara Mishamandani

Scientists and regulators from around the world met to review progress in human carcinogenesis safety evaluation strategies and cancer risk assessment May 16-17 at the Moving Forward in Human Cancer Risk Assessment in the Genomics Era 2.0 *(http://www.hesiglobal.org/i4a/pages/index.cfm?pageid=3607)* workshop held at the OECD (Organisation for Economic Co-operation and Development) Congress Centre in Paris. The meeting was co-sponsored by NIEHS.

Auerbach (second from left) discussed integrating genomics in carcinogenicity testing during his presentation. (Photo courtesy of Rene Reijnders, Maastricht University)

Scott Auerbach, Ph.D., a molecular toxicologist with the National Toxicology Program and NIEHS-funded Superfund Research Program (SRP) grantee Ivan Rusyn, M.D., Ph.D., a professor of environmental sciences and engineering at the Gillings School of Global Public Health at the University of North Carolina at Chapel Hill, were among the speakers at the meeting. Richard Paules, Ph.D., the Molecular Genomics Core director at NIEHS, was one of the organizers of the workshop and served as session chair, roundtable discussion leader, and presenter of the meeting summary. They joined representatives of the academic and industry safety assessment communities, government regulators, and risk assessors from the U.S., European Union, and Japan.

Rusyn used his NIEHS-funded research to explain how to combine biological and chemical information to better understand human toxicity. (Photo courtesy of Rene Reijnders, Maastricht University)

"Getting regulators, toxicologists, and informaticians to talk to each other, and translate paradigms and views across knowledge domains, helps advance the goals of 21st century toxicology," said Auerbach. "One of the things you really notice at meetings like this one is that there are people with problems without solutions — regulators and toxicologists — and people with solutions without problems — informaticians — finding each other and later working together to find a solution that works across multiple domains. In many ways, the meeting was a reflection of the cross-disciplinary nature of the toxicological sciences in today's world."

Expanding the boundaries of toxicogenomics

Rusyn presented a vision for effectively integrating data to facilitate hazard characterization. He discussed how to combine gene expression data with chemical information to improve predication of drug and chemical toxicity.

The number of toxicogenomic studies that incorporate dose-response and population-based designs is on the rise, and the applicability of such data to hazard assessment is increasing. Rusyn described a user-friendly computational approach for dose-response analysis of gene expression data at the pathway level. He also suggested that the challenge of understanding inter-individual differences in toxicity may be met through a combined analysis of toxicity phenotypes and gene expression data from genetically diverse, recombinant inbred mice.

"This meeting afforded a unique opportunity for a candid conversation with practitioners and regulators about the value of genomics in decision-making with respect to human health assessments of drugs and environmental chemicals," said Rusyn. "A real opportunity exists for moving the field of human health risk assessment into the future, by expanding the use of omics beyond heatmaps and network diagrams."

Moving cancer risk assessment forward

The driving force of the workshop was the need to improve human cancer risk assessment with better assessment approaches, assays, exposure estimates, and decision trees, so that toxicologists can ultimately use fewer animals in testing and provide more reliable information concerning human risk.

The current safety paradigm for assessing carcinogenic properties of drugs, cosmetics, industrial chemicals, and environmental exposures relies mainly on *in vitro* genotoxicity testing, followed by two-year rodent bioassays. This testing battery is extremely sensitive, but has low specificity. Rodent bioassays are also associated with high costs, high animal burden, and limited predictive value for human risks. Workshop participants discussed developing alternative testing strategies for carcinogenicity, with emphasis on potential contributions from omics technologies.

“As pointed out by one of the participants, there was a recognition and acknowledgement that advances in technology, that will revolutionize human cancer risk assessment, are coming, some of which are here now, and are unstoppable,” said Paules.

(Sara Mishamandani is a research and communication specialist for MDB Inc., a contractor for the NIEHS Superfund Research Program and Division of Extramural Research and Training.)

Paules, center, speaks during a roundtable discussion. The panel focused on what needs to be done to achieve broad applicability of toxicology studies. Shown, left to right, are Christopher Portier, Ph.D., U.S. Centers for Disease Prevention and Control (retired); Jan Willem Van der Laan, Ph.D., Medicines Evaluation Board; Paules; Carole Yauk, Ph.D., Health Canada; and Nathalie Delrue, Ph.D., OECD. (Photo courtesy of Rene Reijnders, Maastricht University)

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